Galectins constitute an evolutionary conserved family of \( \beta \)-galactoside-binding proteins, ubiquitous in mammals and other vertebrate taxa, invertebrates, and fungi. Since their discovery in the 1970s, their biological roles, initially understood as limited to recognition of carbohydrate ligands in embryogenesis and development, have expanded in recent years by the discovery of their immunoregulatory activities. A gradual paradigm shift has taken place in the past few years through the recognition that galectins also bind glycans on the surface of potentially pathogenic microbes, and function as recognition and effector factors in innate immunity. Further, an additional level of functional complexity has emerged with the most recent findings that some parasites “subvert” the recognition roles of the vector/host galectins for successful attachment or invasion.

**Keywords** Pattern recognition receptors • Galectins • \( \beta \)-Galactoside • Carbohydrate recognition domain • Glycans • Structure • Function • Proto-type • Chimera • Tandem-repeat

1 Introduction

Complex carbohydrate structures encode information that modulates interactions between cells, or cells and the ECM, by specifically binding to carbohydrate-binding proteins such as galectins, formerly known as S-type lectins [Gabius 1997, and references therein]. Galectins constitute an evolutionary conserved family of \( \beta \)-galactoside-binding proteins, ubiquitous in eukaryotic taxa, including the parazoa (sponges) and both protostome and deuterostome lineages of metazoans, and fungi (Cooper 2002; Vasta et al. 1999). Two properties are required in a protein for its inclusion in the galectin family: (a) a characteristic affinity for \( \beta \)-galactosides, and...
(b) a conserved carbohydrate recognition domain (CRD) sequence motif. Based on structural features, galectins have been classified in three types: “proto”, “chimera”, and “tandem-repeat” (TR) (Fig. 1) (Hirabayashi and Kasai 1993). Proto-type galectins (Fig. 1a(a); Fig. 1b) contain one CRD per subunit and are non-covalently linked homodimers. The chimera galectins (Fig. 1a(b)) have a C-terminal CRD and an N-terminal domain rich in proline and glycine. In TR galectins (Fig. 1a(c)) two CRDs are joined by a functional linker peptide. Recently, a novel TR-type galectin with four CRDs has been described (Tasumi and Vasta 2007). The dimerization of proto-type galectins is critical for their function in mediating cell–cell or cell–ECM interactions (Gabius 1997), and similar interactions via the N-terminus domain have been proposed for the chimera galectins (Colnot et al. 1997; Rabinovich et al. 2002). Proto- and TR-types comprise several distinct galectin subtypes. Galectin subtypes have been numbered following the order of their discovery, and so far, 15 have been described in mammals. Galectins-1, -2, -5, -7, -10, -11, -13, -14, and -15 are proto-type. Galectin-3 is the only chimera-type. Galectins-4, -6, -8, -9, and -12 are TR-type. Lower vertebrates and invertebrates appear to have a smaller galectin repertoire. Although galectins lack a typical secretion signal peptide, they are present not only in the cytosol and the nucleus, but also in the extracellular space (Cooper 2002) (Fig. 2). From the cytosol, galectins may be targeted for secretion by non-classical mechanisms, possibly by direct translocation across the plasma.

Fig. 1 Galectin types and structure of the galectin-1/LacNAc complex. a Galectins are classified in three types: “proto” (a), “chimera” (b), and “tandem-repeat” (c); b The structure of the galectin-1/thiodigalactoside (TDG) complex reveals a dimer, which each globular subunit binding a single oligosaccharide

2 Structure and Biochemical Properties of Galectins

The structure of galectin-1 (Liao et al. 1994; Blanchet et al. 2000) complexed with a di-galactoside (Fig. 1b) shows a jellyroll topology typical of legume lectins. The subunit of galectin is composed of an 11-strand antiparallel β-sandwich and contains one CRD. The 3-D structure of the galectin–ligand complex allowed us to identify amino acids that participate in interactions with ligands, as well as the position and orientation of the sugar hydroxyls that interact with the amino acids (Liao et al. 1994; Blanchet et al. 2000).

Most galectins are non-glycosylated soluble proteins, although a few recently discovered exceptions have transmembrane domains (Lipkowitz et al. 2004; Gorski et al. 2002). The presence of a galectin fold in the protistan parasite Toxoplasma gondii, and galectin-like proteins in the fungus Coprinopsis cinerea and in the sponge Geodia cydonium reveals the early emergence and structural conservation of galectins in eukaryotic evolution (Saouros et al. 2005; Walser et al. 2005; Stalz et al. 2006). In contrast, galectin-like proteins such as the lens crystallin protein galectin-related inter-fiber protein (GRIFIN) and the galectin-related protein (GRP) (previously HSPC159; hematopoietic stem cell precursor) lack carbohydrate-binding activity, and are considered products of evolutionary co-option (Ogden et al. 1998; Ahmed and Vasta 2008). The primary structures and gene organization of mammalian galectins are substantially conserved. Prior to or during early in chordate
evolution, duplication of a mono-CRD galectin gene would have led to a bi-CRD galectin gene, in which the N- and C-terminal CRDs subsequently diverged into two different subtypes, defined by exon–intron structure (F4-CRD and F3-CRD). All vertebrate single-CRD galectins belong to either the F3- (e.g., gal-1, -2, -3, -5) or F4- (e.g., gal-7, -10, -13, -14) subtype, whereas TR galectins such as gal-4, -6, -8, -9, and -12 contain both F4 and F3 subtypes (Houzelstein et al. 2004).

Galectins are ß-galactoside-binding lectins, and their preferred ligands are N-acetyllactosamine (LacNAc; Galß1,4GlcNAc) and related disaccharides, with dissociation constants in the order of $10^{-5}$ M (Schwarz et al. 1998; Dam and Brewer 2008). Binding specificities of galectins for lactose (Lac), LacNAc, T-disaccharide (Galß1,3GalNAc) and the human blood group A-tetrasaccharide, together with the presence of amino acid residues that interact with the carbohydrate ligands, have enabled classification of their CRDs into “conserved” or “variable” types (Ahmed and Vasta 1994). The crystal structure of the galectin-1 (conserved type) complexed with a di-galactoside determined at 1.9 Å resolution (Fig. 1b) revealed the galectin structural fold, and allowed the identification of the amino acids involved and the hydroxyl groups of the ligands that participate in protein–carbohydrate interactions (Liao et al. 1994; Bianchet et al. 2000; Lobsanov et al. 1993). The carbohydrate-binding site is formed by three continuous concave strands (ß4–ß6) containing all residues involved in direct interactions with LacNac. Additional interactions involving a water molecule that bridges the nitrogen of the NAc group with His$^{52}$, Asp$^{54}$, and Arg$^{73}$ explains the higher affinity of LacNAc over Lac. Unlike galectin-1, galectin-3 has an extended carbohydrate-binding site formed by a cleft open at both ends, in which the LacNAc is positioned in such a way that the reducing end of the LacNAc (GlcNAc) is open to solvent, but the non-reducing moiety (Gal) is in close proximity to residues in the ß3 strand (Seetharaman et al. 1998). The extended binding site leads to increased affinity for glycans with multiple lactosamine units, and with their substitution of the non-reducing terminal galactose moiety with ABH blood group oligosaccharides [Fucα1, 2; GalNAcα1,3(Fucα1,2); and Gaia1,3(Fucα1,2)]. For the nematode *Caenorhabditis elegans* 16-kDa galectin (variable type), the shorter length of the loops connecting the three ß4–ß6 strands determines its broader binding specificity for blood group precursor oligosaccharides. Therefore, although galectins are considered a conserved lectin family, most metazoans are endowed of a complex galectin repertoire, with members exhibiting multiple isoforms and more or less subtle variations in carbohydrate specificity, which together with a certain degree of plasticity in sugar binding of each CRD, suggests a substantial diversity in recognition properties (Sparrow et al. 1987; Sato and Hughes 1992; Ahmed et al. 2002; Shoji et al. 2003; Zhou and Cummings 1990; Fang et al. 1993).

Thermodynamic approaches have been used not only to assess the galectins’ carbohydrate-binding properties, but also the oligomeric organization of the protein. On microcalorimetric studies, the dissociation constants for the interactions of bovine galectin-1 with the preferred ligands (Lac, N-acetyllactosamine, thiodigalactoside) were in the range of $10^{-5}$ M, with two binding sites per molecule (Schwarz et al. 1998). Although galectin and legume lectins display a striking similarity in their 3-D structures, the thermal stability of the galectin is different from that of
concanavalin A (Con A). Like Con A, the bovine galectin exists as a tetramer at the denaturation temperature, but, unlike Con A, it does not dissociate upon unfolding (Schwarz et al. 1998).

### 3 Biological Roles of Galectins in Development and Regulation of Immune Homeostasis

Galectins were initially thought to only bind endogenous (“self”) glycans and mediate developmental processes, including cell differentiation and tissue organization, and more recently, regulation of immune homeostasis (Leffler et al. 2004, Yang et al. 2008) (Fig. 3). In the past few years, however, it has become clear that galectins also bind glycans on the surface of potentially pathogenic microbes and parasitic worms, and mediate recognition and effector functions in innate immunity (Sato and Nieminen 2004). Glycans that contain N-acetyllactosamine and polylactosamine chains [(Galβ1,4GlcNAc)n], such as laminin, fibronectin, lysosome-associated membrane proteins, and mucins, are the preferred endogenous ligands for mammalian, bird, and amphibian galectins (Seetharaman et al. 1998; Sparrow et al. 1987; Sato and Hughes 1992; Ahmed et al. 2002; Shoji et al. 2003; Zhou and Cummings 1990; Fang et al. 1993). The biological function of a particular galectin, however, may vary from site to site, depending on the availability of suitable ligands. The binding properties and biological functions of galectins in the oxidative extracellular environment, however, may depend on their immediate binding to ligand, which prevents the oxidation of free cysteine residues, as well as galectin

**Fig. 3** Biological roles of galectins upon binding to the cell surface. Galectins can bind to glycans on neighboring cells or to cells and the extracellular matrix, leading to cell adhesion, or to the surface of a single cell resulting in the formation of lattices, and the activation of signaling pathways.
susceptibility to proteolysis (Liao et al. 1994; Lobsanov et al. 1993). The binding of galectins to cell surface β-galactoside-containing glycolipids and glycoproteins can lead to the formation of lattices that cluster these ligands into lipid raft micro-domains required for optimal transmission of signals relevant to cell function (Rabinovich et al. 2007b; Brewer et al. 2002; Partridge et al. 2004) (Fig. 4). In solution galectins can form multivalent species in a concentration-dependent equilibrium (Morris et al. 2004). Proto-type galectins associate as non-covalently bound dimers via a hydrophobic interphase, whereas galectin-3 associates via its N-terminal domain to form oligomers that in the presence of multivalent oligosaccharides in solution or at the cell surface display binding cooperativity (Dam and Brewer 2008; Brewer et al. 2002). The bivalent TR-type galectins can recognize different saccharide ligands with a single polypeptide, although they can also form higher order aggregates that enhances their avidity. Galectin-mediated lipid raft assembly may modulate turnover of endocytic receptors, signal transduction pathways leading to T-cell activation and cytokine secretion, or apoptosis, B-cell maturation, activation and tolerance, and neutrophil activation leading to phagocytosis, oxidative burst, and protease and cytokine release. Thus, galectin-glycoprotein lattices at the cell surface have been proposed to function as an “on-an-off switch” that regulates cell proliferation, differentiation and survival, including immune cell responsiveness and tolerance (Dam and Brewer 2008; Brewer et al. 2002).

Since their discovery, galectins have been proposed to participate in embryogenesis, development, and neoplasia. This has been based on their binding to “self” carbohydrate moieties, such as polylactosamine-containing glycans, abundant at the cell surface and the ECM (Fig 3). Chicken galectins have been proposed to participate in myoblast fusion, whereas murine galectin-1 and galectin-3 would have roles in notochord development, somitogenesis, and development of muscle tissue and central nervous system (Cooper et al. 1991; Watt et al. 2004; Georgiadis et al.
2007; Fowlis et al. 1995). Despite the increasing availability of genetically modified mice, however, strains carrying null mutations for some galectins have failed to display overt developmental phenotypes (Colnot et al. 1998; Puche et al. 1996; Colnot et al. 2001). Thus, other genetically tractable model organisms endowed with a less diversified galectin repertoire such as *Drosophila* and zebrafish have become attractive alternatives for these selected galectins, with promising results (Pace et al. 2002; Ahmed et al. 2004).

In the past few years it has been shown that galectins participate in regulation of both innate and adaptive immunity (Vasta 2009; Rabinovich et al. 2002; van Die and Cummings 2010). The recently proposed roles of galectins in immune functions have been further supported by their ability to directly recognize microbial pathogens (Vasta 2009), a property well characterized for other lectin types, such as C- and F-lectins, ficolins, and pentraxins. Although the roles of lectins in non-self recognition are particularly critical in invertebrates, since these organisms lack immunoglobulins and rely solely in innate immune mechanisms for recognition of potential microbial pathogens (Vasta et al. 1999), susceptibility/resistance to several infectious diseases in humans are determined by the presence of certain lectin alleles (Dias-Baruffi et al. 2010). Galectins from both invertebrates and vertebrates recognize a variety of viral and bacterial pathogens and protozoan parasites (Reviewed in Vasta 2009).

Galectins are ubiquitously expressed and distributed in mammalian tissues, including most cells of the innate (dendritic cells, macrophages, mast cells, natural killer cells, gamma/delta T cells, and B-1 cells) and adaptive (activated B and T cells) immune system, and as in other cell types (Stowell et al. 2008; Rabinovich et al. 2007a). Since the early 1990s a growing body of experimental (*in vivo* and *in vitro*) evidence has accumulated to support the roles of galectins expressed by these cells and neighboring stromal cells in the development and regulation of innate and adaptive immunity homeostasis as well as responses to infectious and allergic challenge, and cancer. Galectins released by stromal cells in central compartments contribute to the differentiation of immune cell precursors. Immune challenge and several pathological conditions, may lead to further activation and differentiation of immune cells, and modulate the expression and release of galectins to the extracellular space where they may have autocrine or paracrine effects on immune regulation. Galectins released by immune cells can oligomerize and form lattices at the cell surface leading to activation of transmembrane signaling pathways that modulate immune cell functions, including for example, cell adhesion and migration, T-cell apoptosis, and the Th1/Th2 cytokine balance (Rabinovich et al. 2002, 2007a, 2007b). Further, galectins released into the extracellular environment under abnormal situations may constitute “danger signals”, or by exerting their activities on other cells, such as mast cells, induce degranulation and release of factors (e.g., histamine) that represent the “danger signals” leading to activation of immune mechanisms in the absence of antigenic challenge (Sato and Nieminen 2004).

Galectins have diverse effects on cells involved in innate immune responses, including macrophages and dendritic cells, neutrophils, eosinophils, and mast cells. Galectin-1 participates in acute and allergic inflammation and displays anti-inflam-
matory activities by blocking or attenuating signaling events that lead to leukocyte infiltration, migration, and recruitment (Stowell et al. 2008). It also displays various other effects on innate immunity, including cell surface exposure of phosphatidylserine in activated neutrophils, a process that leads to neutrophil removal by phagocytic cells without causing apoptosis, and activation/deactivation of macrophages on a concentration-dependent manner. In contrast to the anti-inflammatory effects of galectin-1, galectin-3 shows pro-inflammatory activity. Galectin-3 is normally expressed in various epithelia and inflammatory cells, such as activated macrophages, dendritic cells, and Kupffer cells, and is upregulated during inflammation, cell proliferation, and cell differentiation. Galectin-3 also exhibits anti-apoptotic activity for macrophages and enhances their interactions with basal lamina glycans, such as laminin and fibronectin. Taken together, these observations strongly suggest that galectin-3 enhances macrophage survival, and positively modulates their recruitment and anti-microbial activity. Galectin-9 is a selective chemoattractant for eosinophils, highly expressed in various tissues of the immune system, such as bone marrow, spleen, thymus, and lymph nodes. Gal-9 released from activated T cells induces chemotaxis, activation, oxidative activity, and degranulation of eosinophils, and monocyte-derived DC maturation (Stowell et al. 2007; Zuñiga et al. 2001; Liu and Hsu 2007; Hirashima et al. 2004).

Concerning adaptive immune responses, galectins have been proposed as regulators of immune cell homeostasis (Rabinovich et al. 2002). Interactions between stromal cells from the bone marrow and thymic compartments and lymphocyte precursors are critical to their development, selection, and further progression to the periphery. In this regard, interactions mediated by galectins can modulate B-cell maturation and differentiation both at the central and peripheral immune compartments (Rossi et al. 2006) Similarly, from their early developmental stages in the thymic compartment to the removal of the mature activated T cells in the periphery, the regulation of T-cell survival is critical to a controlled immune response. Galectin-1 can regulate T-cell proliferation and apoptosis through binding and clustering of lactosamine-rich cell surface glycoconjugates into segregated membrane microdomains (Rabinovich et al. 2007b). Galectin-1 may have pro- or anti-apoptotic effects on T cells depending on the developmental stage and activation status of the cell, and the microenvironment in which the exposure takes place. The effects of galectin-3 in T-cell survival, however, are dependent on whether protein is produced endogenously (anti-apoptotic) or by exogenous exposure (pro-apoptotic) (Liu and Hsu 2007). Galectins also exert regulatory functions in T-cell homeostasis, and signaling cascades triggered by their binding and lattice formation at the T-cell surface has implications in a variety of downstream events that modulate their differentiation, functional activation, and production of pro- and anti-inflammatory cytokines. The effects of galectins on T-cell cytokine synthesis and secretion ultimately determines the Th1/Th2 polarization of the immune response. By reducing IFN-γ and IL-2 and enhancing IL-5, IL-10, and TGF-β production, galectin-1 skews the balance from a Th1- toward a Th2- polarized response, whereas by reducing IL-5 levels, galectin-3 has the opposite effect (Yang et al. 2008). Finally, given the regulatory roles of galectins on cells that mediate both innate and adaptive immune re-
sponses, their effects can be beneficial or detrimental to pathological conditions that have a basis on exacerbated or depressed immune function, such as inflammatory, allergic and autoimmune disorders, and cancer (Yang et al. 2008).

4 Galectins as Pattern Recognition Receptors

Recently, galectins have been discovered to bind glycans on the surface of viruses, bacteria, protista, and fungi (reviewed in Vasta 2009). Thus, the potential role of galectins as pattern recognition receptors (PRRs) has become an area of increased attention. Furthermore, the considerable diversity of the galectin repertoire in each organism and the substantial or subtle variations in the specificity of each galectin towards the target glycans, which are determined by oligosaccharide repeats, branchings or substitutions, suggest that there is extensive diversity and plasticity in the capacity of galectins for non-self recognition. The presence of canonical and extended CRDs, and the carbohydrate-independent binding properties of the N-terminus region of galectin-3, further suggests that galectins have a substantially diversified recognition capacity. Moreover, because galectins from all three types (proto, chimera, or TR) can form oligomers, their multivalent binding properties, including increased avidity, clearly enable galectins to participate effectively both in direct recognition of pathogens and parasites, and downstream processes that lead to modulation of innate and adaptive immune responses. Whether galectin-mediated recognition is an effective defence mechanism with a clear benefit for the host is not entirely clear, except for a few examples. It is noteworthy that a particular glycan on the surface of a microorganism or parasite can be recognized by multiple galectins, and that the outcome of the interaction differs considerably depending on the galectin type involved and the concentration of the galectin in a particular cell surface or extracellular microenvironment. This, in turn, determines the level of oligomerization and cooperative binding to ligand, and the potentially antagonistic or synergistic activation of pathogen signaling pathways (e.g., modulation of immune activation, or cytokine production and secretion) (Rabinovich et al. 2007b).

5 Some Microbial Pathogens and Parasites Subvert the Role of Galectins as PRRs

In some cases, the microbe’s recognition by the vector or host galectins promote its adhesion, host cell entry, or infection persistence, in addition to modulating the host’s immune responses. Thus, these pathogens and parasites would “subvert” the roles of host or vector galectins as PRRs, to attach to or gain entry into their cells. This is clearly illustrated by the participation of galectin interactions in the infection mechanisms of HIV. In contrast to the inhibitory role of galectin-1 in paramixovi-
rus-mediated cell fusion, galectin-1, which is abundant in organs that represent major reservoirs for HIV-1, such as the thymus and lymph nodes, promotes infection by HIV-1 by facilitating viral attachment to CD4 receptor, and increasing infection efficiency (Ouellet et al. 2005; Mercier et al. 2008). Recent studies showed that galectin-1 enhances HIV adsorption kinetics on monocyte-derived host macrophages, which facilitates HIV-1 infectivity by shortening the time required to establish an infection. Further, galectin-1 would also function as a soluble scavenger receptor and enhance the uptake of the virus by macrophages, which together with evidence that galectin-1 is present in the ejaculate and the heads and tails of late spermatids, led to extend the proposal that galectin-1 may also facilitate sexual transmission of HIV-1 (Mercier et al. 2008). This would take place through enhancement of viral adsorption kinetics on the target cells’ surface by the galectin-1 released by sheared fibroblasts and epithelial cells following sex-related micro-abrasions. Gal-3 has no effect on HIV-1 adsorption, entry, or infection, although its expression is upregulated by the HIV Tat protein in several human cell lines, and in cells infected with other retroviruses, suggesting that it may participate in regulation of antiviral immunity (Fogel et al. 1999; Schroder et al. 1995; Hsu et al. 1996). This underscores the relevance of the subtle differences in galectin specificity and affinity that may determine very different recognition and effector outcomes. It is noteworthy that HIV also uses recognition by DC-SIGN, a C-type lectin, to enter dendritic cells, thereby underscoring the multiple adaptations of the viral glycome for host infection (Ouellet et al. 2005; Mercier et al. 2008).

*Leishmania* species, which spend part of their life cycle in phlebotomine sandflies that constitute vectors for transmission to the vertebrate hosts, are also illustrative examples. Upon the sandfly feeding on blood from an infected host, the ingested amastigotes mature into promastigotes, which attach to the insect midgut epithelium to prevent their excretion along with the digested bloodmeal, and undergo numerous divisions before differentiating into free-swimming infective metacyclics (Kamhawi 2006). Although the involvement of the parasite LPG in this interaction had been suspected from prior studies, the specific *Phlebotomus papatasi* sandfly midgut receptor for the procyclic *L. major* LPG was identified as a 35.4-kDa TR galectin (PpGalec) only expressed by epithelial midgut cells, and upregulated in the blood-feeding females (Kamhawi et al. 2004). Because the binding specificity of PpGalec is restricted to *Leishmania* promastigotes bearing poly-Gal(β1-3) side chains on their LPG, it was proposed that it is the carbohydrate moiety responsible for specific binding of *L. major* to *P. papatasi* midgut linings. The assembly of polygalactose epitopes is downregulated during *L. major* metacyclogenesis, and thus, unable to bind to rPpGalec the free-swimming infective metacyclic promastigotes are released from the midgut for transmission from the sandfly to the mammalian host (Kamhawi et al. 2004).

The protozoan parasite *Perkinsus marinus* is a facultative intracellular parasite that causes “Dermo” disease in the eastern oyster *Crassostrea virginica*, and is responsible for catastrophic damage to shellfisheries and the estuarine environment in North America (Harvell et al. 1999). The infection mechanism remains unclear, but it is likely that while filter feeding, the healthy oysters ingest *P. marinus* trophozoites
released to the water column by the infected neighboring individuals. Inside oyster phagocytic cells (hemocytes), trophozoites resist oxidative killing, proliferate, and spread throughout the host. It was recently discovered that oyster hemocytes recognize *P. marinus* via a novel galectin (CvGal) that displays four canonical galectin CRDs, a domain organization unlike any of the known galectin types (Tasumi and Vasta 2007). Two amino acid residues (His53 and Asp55) that interact with the NAc group via a water molecule are missing in all four CvGal CRDs resulting in broader carbohydrate specificity. CvGal is present in the cytoplasm of circulating granulocytes, and upon their attachment and spreading it is translocated to the periphery, secreted, and binds to the cell surface. The remaining galectin is released to the extracellular environment, where it may bind to all other circulating (non-activated) granulocytes and hyalinocytes. The most surprising observation, however, was that the soluble CvGal also binds in a carbohydrate-specific manner to a wide variety of microorganisms, phytoplankton components, and preferentially, to *Perkinsus* spp trophozoites, suggesting a direct role in recognition and opsonization of potential microbial pathogens, as well as algal food. The partial inhibition of phagocytosis of *P. marinus* trophozoites by pre-treatment of hemocytes with anti-CvGal revealed that the hemocyte surface-associated CvGal is a phagocytosis receptor for *P. marinus*. Thus, *P. marinus* may have evolved to adapt the trophozoite’s glycocalyx to be selectively recognized by the oyster hemocyte CvGal, thereby subverting the oyster’s innate immune/feeding recognition mechanism to gain entry into the host cells (Tasumi and Vasta 2007) (Fig. 4).

A recent study identified galectin-1 as the receptor for the protozoan parasite *T. vaginalis* (Okumura et al. 2008) the causative agent of the most prevalent non-viral sexually transmitted human infection in both women and men. As an obligate extracellular parasite, establishment and persistence of *T. vaginalis* infection requires adherence to the host epithelial cell surface. Like *Leishmania* spp, *T. vaginalis* displays a surface LPG rich in galactose and N-acetyl glucosamine, which is recognized in a carbohydrate-dependent manner by galectin-1 expressed by the epithelial cells in the cervical linings, as well as placenta, prostate, endometrial, and decidual tissue, also colonized by the parasite (Okumura et al. 2008).

### 6 Conclusions

Recent studies clearly indicate that galectins can function as PRRs that target lactosamine-containing oligosaccharides on the surface of virus, bacteria, protista, and helminth pathogens and parasites. A perplexing paradox arises, however, by the fact that galectins also recognize lactosamine-containing glycans on the cell surface of the host for development and regulation of immune homeostasis. According to the Medzhitov and Janeway model (2002) for non-self recognition, PRRs recognize pathogens via highly conserved microbial surface molecules of wide distribution such as lipopolysaccharide or peptidoglycan (pathogen-associated molecular patterns [PAMPs]), which are absent in the host. Hence, this would not rigorously apply
to galectins, which apparently bind the same self/non-self molecular pattern. This paradox underscores first, an oversimplification in the use of the PRR/PAMP terminology, which although it has been useful and is currently widespread, it should be used with great caution. Second, and most importantly, it reveals the significant gaps in our knowledge about the actual diversity in recognition of the host galectin repertoire, and the dynamic and mechanistic aspects of the subcellular compartmentalization and secretion of its components, as well as the detailed structural and biological aspects of their interactions with the microbial carbohydrate moieties. The microbial and host glycomes and their receptors continuously evolve to escape mutual recognition, a process known as the “Red Queen effect” (Varki 2006), by which the microbe avoids recognition by the host innate immune receptors (PRRs) and, the host by the microbial colonization factors (agglutinins, adhesins, and lectins). Given the key roles played by galectins in host development and immunoregulation by the recognition of “self” lactosamine moieties, strong functional constraints would prevent galectins from dramatic evolutionary changes in carbohydrate specificity, which is to some extent supported by the apparent structural conservation within this lectin family. Further, with the current evidence about how pathogens and parasites, which display a remarkable evolutionary plasticity, efficiently subvert the roles of galectins to attach or gain entrance into the host cells, it seems more plausible that instead of avoiding recognition by the host, they would have evolved their glycomes to mimic their hosts’ in a “Trojan horse” model (Tasumi and Vasta 2007), and rely on the host’s self-recognition molecules such as galectins for attachment to the vector or host invasion. It is noteworthy that most of (if not all) these pathogens and parasites are endowed with diverse and powerful mechanisms to evade intracellular killing by the host, and/or down-regulate downstream immune responses. The complex strategies developed by microbial pathogens to successfully colonize, enter, proliferate, and disseminate within and among their vectors or hosts, are the products of strong selective pressures that have led to adaptations that ensure their survival in the most hostile environment of all, and thus represent a significant challenge for the development of novel strategies for intervention in human disease.

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